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Regioselective Alkoxysulfenylation of Aryl Methyl Ureas using Alkoxycarbonylsulfenyl Chloride

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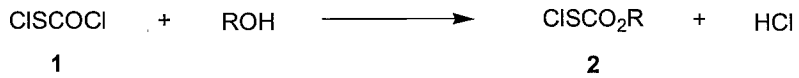
Abstract

N^1-Aryl-N^2-methylureas (ArN^1HCON^2HMe) were regioselectively alkoxysulfenylated using alkoxycarbonylsulfenyl chloride ($ClSCO_2R$) under two alternative reaction conditions; the reaction proceeded at N^2-position in the absence of base, whereas the use of NaH promoted the reaction at N^1-position.

I. Introduction

Chlorocarbonylsulfenyl chloride (**1**) and alkoxycarbonylsulfenyl chloride (**2**), prepared from **1** and ROH, are a set of unique and readily available ambident electrophilic reagents (Scheme 1).[1] Zumach's group originally exploited reagents **1** and **2**, which have been utilized for the synthesis of heterocyclic compounds containing sulfur, oxygen, and nitrogen, and reviewed their impressive highlights.[2] Another utility was performed for a protecting agent for sulfanyl group in the peptide chemistry.[3]



As a part of our longstanding interest in *S,N*-containing heterocycles,[4] we previ-

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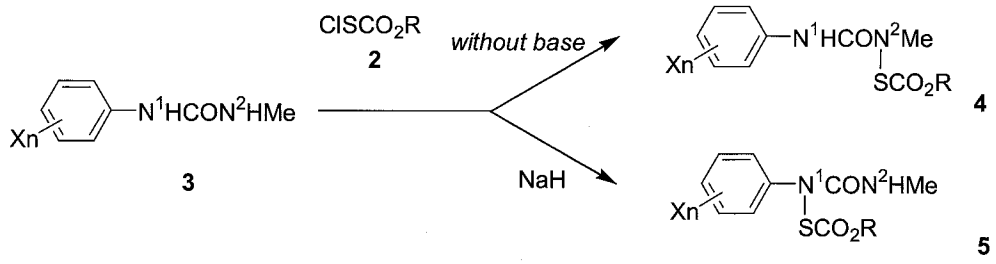
ously reported regioselective α-methoxycarbonylsulfenylation of ketones and aldehydes and application to a versatile method for preparing thiazolones, thiadiazinones, and 3-indolethiols.[5] As a further extension, we report here a couple of regiocoselective N-alkoxycarbonylsulfenylations of N^1-Aryl-N^2-methylureas (ArN^{1}HCON^{2}HMe) **3** using **2** to afford N^2-alkoxycarbonylsulfenylureas **4** and N^1-isopropoxycarbonylsulfenylureas **5** (Scheme 1).

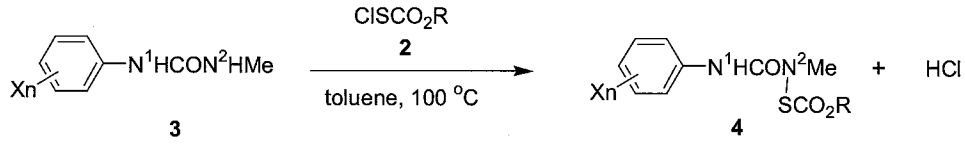
Scheme 1



II. Results and Discussion

First, the alkoxycarbonylsulfenylation of **3** using **2** in the absence of bases was examined. The reaction proceeded at the N^2-position with high regioselectively to give **4** under heating conditions (toluene, 100°C). This result is probably owing to the higher inherent nucleophilicity of N 2 than that of N 1. Table 1 lists the successful results of the present method using several reagents **2** and substrates **3**, which have a specific substitution pattern (3-CF_3, 3,4-Cl_2, and 2-F) expecting for the phenyl urea-type herbicidal activity.[6] Indeed, these reactions produced the desired compounds **4a-e** each as a sole regioisomer in moderate to good yields. But, particular correlation was not observed between structures of **2** or **3** and the yields.

Table 1

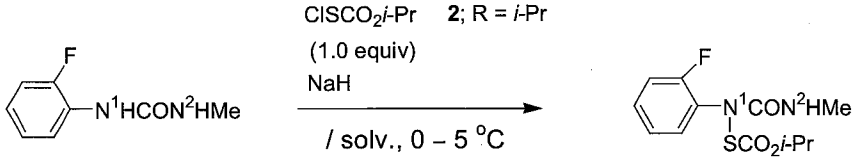


entry	Xn	R	Product	yield/%	entry	Xn	R	Product	yield/%
1	3-CF_3	Me	**4a**	45	4	2-F	Et	**4d**	65
2	3,4-Cl	Et	**4b**	42	5		*i*-Pr	**4e**	57
3		*i*-Pr	**4c**	62					

Second, regioselective (region complementaly) N^1-sulfenylation was investigated.

A pertinent patent disclosed that a 2-F analogue, N^1-alkoxycarbonylsulfenyl-N^2-(2'-fluorophenyl)-N^2-methylureas, had potent and selective phenyl urea type herbicidal activity.[7] Thus, we focus our attention on the reaction using the urea **3** (Xn=F). Treatment of **3** with NaH resulted in a regioselective anion formation on N^1-position due to the higher acidity than that of N^2-position. Higher nucleophilic N^1-anion switched the regioselectivity to produce N^1-alkoxysulfenyl-N^1-(2'-fluorophenyl)-N^2-methylureas **5a** in clear contrast to the reaction without bases as mentioned before. Table 2 lists the successful results. Solvent screening showed that DMF was superior than CH_3CN and THF. Highest yield (53%) was obtained when 1.5 equiv of the urea and 1,6 equiv of NaH was used.

Table 2



5a

entry	urea/eq.	NaH/eq.	solvent	yield/%
1	1.1	1.2	CH_3CN	trace
2			THF	11
3			DMF	30
4	1.5	1.6		53
5	2.0	2.1		28
6	0.5	0.5		21[a]

a) Based on $ClSCO_2i$-Pr

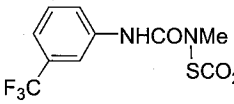
In conclusion, we performed regioselective N^1- and N^2-alkoxysulfenylations of N^1-Aryl-N^2-methylureas. Further investigation of herbicidal activity and its structure-activity relationship of these synthesized compounds is under progress.

III. Experimental

Flash column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM). Melting points were determined on a hot stage microscope apparatus (Yanagimoto) and were uncorrected. NMR spectra were recorded on a JEOL DELTA 300 spectrometer, operating at 300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR. Chemical shifts (δppm) in $CDCl_3$ were reported downfield from TMS (=0 ppm) for ^1H NMR. For ^{13}C NMR, chemical shifts on a scale relative to (77.00 ppm) as an internal reference. IR Spectra were recorded on a JASCO FT / IR-5300 spec-

trophotometer. Mass spectra were measured on a JEOL JMS-T 100 LC spectrometer.

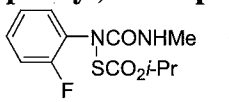
Typical Procedure of N^2-alkoxysulfenylation; exemplified by *N*-(3'-trifluoromethylphenyl)-*N'*-methyl-*N'*-methoxycarbonylsulfenylurea (4a)



$ClSCO_2Me$ (70 mg, 0.55 mmol) was slowly added to a stirred solution of *N*-(2'-trifluoromethylphenyl)-*N'*-methylurea (109 mg, 0.50 mmol) in toluene at 100°C under an Ar atmosphere, followed by being stirred at the same temp. for 2 h. The mixture was cooled and concentrated to give crude oil, which was purified by SiO_2-column chromatography (hexane: AcOEt=15: 1) to give the desired product (**4a**; 70 mg, 45%).

pale yellow oil; ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.37 (3 H, s), 4.00 (3 H, s), 7.29–7.35 (^{1}H, m), 7.37–7.46 (^{1}H, m), 7.60–7.67 (^{1}H, m), 7.69–7.74 (^{1}H, m), 7.81–7.93 (^{1}H,brs); ^{13}C NMR (75 MHz; $CDCl_3$): δ 40.82, 55.18, 116.28 [d, $^3J(^{13}C, ^{19}F)$=3 Hz], 120.20 [d, $^3J(^{13}C, ^{19}F)$=3 Hz], 122.64, 124.14 [d, $^1J(^{13}C, ^{19}F)$=271 Hz], 129.37, 131.19 [d, $^2J(^{13}C, ^{19}F)$=33 Hz], 138.59, 155.07, 169.01; IR (neat) 3331, 2959, 1740, 1676, 1601, 1541, 1495, 1446, 1336, 1255, 1132 cm^{-1}.

Typical Procedure of N^1-alkoxysulfenylation; exemplified by *N*-(2'fluorophenyl)-*N*-isopropoxycarbonylsulfenyl-*N'*-methylurea (5a)

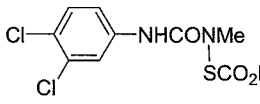


N-(2'-fluorophenyl)-*N'*-methylurea (126 mg, 0.75 mmol) was slowly added to a stirred solution of NaH (60% in oil) (32 mg, 0.80 mmol) in DMF at 0–5°C under an Ar atmosphere. $ClSCO_2i$-Pr (77 mg, 0.50 mmol) was slowly added to the mixture at the same temp., and then warmed up to 20–25°C durring 7 h. Water was added to the mixture, which was extracted three times with Et_2O. The comdined organic phase was washed with water, bribe, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2-column chromatography (hexane: AcOEt=20: 1) to give the desired product (**5a**; 61 mg, 43%).

pale yellow crystals; mp 53–55°C; ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.37 (6 H, d, J=6.5 Hz), 3.29 (3 H, s), 5.10 (^{1}H, sep, J=6.5 Hz), 6.97–7.16 (3 H, m), 8.17–8.26 (^{1}H, m), 11.12–11.20 (^{1}H, br); ^{13}C NMR (75 MHz; $CDCl_3$): δ 21.78, 21.87, 30.69, 71.61, 114.81 [d, $^2J(^{13}C, ^{19}F)$=19 Hz], 121.51, 123.79 [d, $^3J(^{13}C, ^{19}F)$=9 Hz], 124.37 [d, $^4J(^{13}C, ^{19}F)$=4 Hz], 126.61 [d, $^3J(^{13}C, ^{19}F)$=9 Hz], 152.03, 152.98 [d, $^1J(^{13}C, ^{19}F)$=242 Hz], 156.03; IR (KBr) 3221, 2978, 1723, 1620, 1551, 1458, 1356, 1314, 1252, 1186, 1101 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{15}FN_2O_3S$ ($M+Na^+$) 309.0685 found 309.0680.

***N*-(3',4'-dichlorophenyl)-*N'*-methyl-*N'*-ethoxycarbonylsulfenylurea (4 b)**

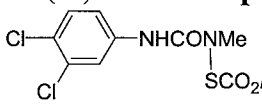
Following the procedure for the preparation of **4a**, the reaction of *N*-(3',4'-



dichlorophenyl)-*N'*-methylurea (110 mg, 0.50 mmol) with $ClSCO_2Et$ (77 mg, 0.55 mmol) gave the desired product (**4b**; 68 mg, 42%).

pale yellow crystals; mp 95–97°C; ^1H NMR (300 MHz; $CDCl_3$): δ 1.36 (3 H, t, J = 7.2 Hz), 3.35 (3 H, s), 4.40 (2 H, q, J = 7.2 Hz), 7.24–7.30 (^1H, m), 7.32–7.38 (^1H, m), 7.63–7.66 (^1H, m), 7.72–7.80 (^1H, brs); ^{13}C NMR (75 MHz; $CDCl_3$): δ 14.30, 40.88, 65.32, 118.82, 121.21, 126.87, 130.35, 132.66, 137.61, 154.94, 168.27; IR (KBr) 3328, 2990, 2936, 1748, 1663, 1580, 1503, 1387, 1294, 1233, 1134 cm^{-1}.

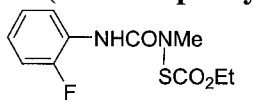
N-(3',4'-dichlorophenyl)-N'-methyl-N'-isopropoxycarbonylsulfenylurea (4c)



Following the procedure for the preparation of **4a**, the reaction of *N*-(3',4'-dichlorophenyl)-*N'*-methylurea (110 mg, 0.50 mmol) with $ClSCO_2i$-Pr (85 mg, 0.55 mmol) gave the desired product (**4c**; 104 mg, 62%).

pale yellow crystals; mp 109–111°C; ^1H NMR (300 MHz; $CDCl_3$): δ 1.34 (6 H, d, J = 6.2 Hz), 3.34 (3 H, s), 5.21 (^1H, sep, J = 6.2 Hz), 7.23–7.29 (^1H, m), 7.31–7.37 (^{1}H, m), 7.61–7.66 (^{1}H,m), 7.71–7.83 (^1H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 21.85, 40.86, 74.27, 118.86, 121.21, 126.75, 130.29, 132.59, 137.63, 155.03, 167.63; IR (KBr) 3301, 2982, 1734, 1661, 1582, 1522, 1476, 1381, 1296, 1173, 1132 cm^{-1}.

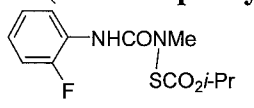
N-(2'-fluorophenyl)-N'-methyl-N'-ethoxycarbonylsulfenylurea (4d)



Following the procedure for the preparation of **4a**, the reaction of *N*-(2'-fluorophenyl)-*N'*-methylurea (84 mg, 0.50 mmol) with $ClSCO_2Et$ (77 mg, 0.55 mmol) gave the desired product (**4d**; 88 mg, 65%).

pale yellow oil; ^1H NMR (300 MHz; $CDCl_3$): δ 1.36 (3 H, t, J = 7.2 Hz), 3.37 (3 H, s), 4.40 (2 H, q, J = 7.2 Hz), 6.95–7.16 (3 H, m), 7.98–8.06 (^1H, br), 8.10–8.19 (^1H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 14.24, 40.82, 65.11, 114.60 [d, $^2J(^{13}C, ^{19}F)$ = 18 Hz], 120.92, 123.55 [d, $^3J(^{13}C, ^{19}F)$ = 8 Hz], 124.48 [d, $^4J(^{13}C, ^{19}F)$ = 3 Hz], 126.64 [d, $^3J(^{13}C, ^{19}F)$ = 8 Hz], 152.57 [d, $^1J(^{13}C, ^{19}F)$ = 241 Hz], 154.90, 168.40; IR (KBr) 3331, 2984, 1742, 1680, 1618, 1595, 1520, 1454, 1318, 1254, 1150 cm^{-1}.

N-(2'-fluorophenyl)-N'-methyl-N'-isopropoxycarbonylsulfenylurea (4e)



Following the procedure for the preparation of **4a**, the reaction of *N*-(2'-fluorophenyl)-*N'*-methylurea (84 mg, 0.50 mmol) with $ClSCO_2i$-Pr (85 mg, 0.55 mmol) gave the desired product (**4e**; 82 mg, 57%).

pale yellow oil; ^1H NMR (300 MHz; $CDCl_3$): δ 1.34 (6 H, d, J = 6.2 Hz), 3.36 (3 H,

s), 5.22 (^{1}H, sep, J=6.2 Hz), 6.95–7.16 (3 H, m), 7.98–8.07 (^{1}H, br), 8.09–8.18 (^{1}H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 21.80, 40.82, 74.04, 114.59 [d, $^2J(^{13}C, ^{19}F)$=20 Hz], 120.96, 123.52 [d, $^3J(^{13}C, ^{19}F)$=9 Hz], 124.46 [d, $^4J(^{13}C, ^{19}F)$=3 Hz], 126.67 [d, $^3J(^{13}C, ^{19}F)$=9 Hz], 152.59 [d, $^1J(^{13}C, ^{19}F)$=241 Hz], 155.00, 167.81; IR (KBr) 3333, 2982, 2936, 1734, 1678, 1537, 1456, 1318, 1258, 1167, 1092 cm^{-1}.

Acknowledgements

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References and Notes

1) Chlorocarbonylsulfenyl chloride (**1**) and alkoxycarbonylsulfenyl chloride (**2**) were commercially available from Tokyo Kasei Kogyo Co., Ltd. and Aldrich Chem. Co., Ltd., respectively. **1** is also easily prepared from Cl_3CSCl and 95% H_2SO_4-H_2O in a large scale: E. Muehlbauer and W. Weiss, German Pat. 1233882 (*Chem. Abstr., 66,* 95023 j, 1967).

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